Medical Drug Clinical Criteria

Subject:	Opdivo Qvantig (nivolumab hyaluronidase-nvhy)		
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Overview

This document addresses the use of Opdivo Qvantig (nivolumab hyaluronidase-nvhy), a programmed death receptor-1 (PD-1) blocking antibody, and hyaluronidase, an endoglycosidase. Opdivo Qvantig may be substituted for intravenous nivolumab. The package insert notes Opdivo Qvantig (nivolumab and hyaluronidase-nvhy) is not indicated in combination with ipilimumab.

The following are the FDA indications for Opdivo Qvantig.

Renal Cell Carcinoma

- in those with intermediate or poor risk advanced RCC, as a first-line treatment following combination treatment with intravenous nivolumab and ipilimumab.
- In those with advanced RCC, as a first-line treatment in combination with cabozantinib.
- In those with advanced RCC who have received prior anti-angiogenic therapy.

Melanoma

- In those with unresectable or metastatic melanoma.
- In those with unresectable or metastatic melanoma following combination treatment with intravenous nivolumab and ipilimumab.
- For the adjuvant treatment in those with completely resected stage IIB, stage IIC, Stage III, or Stage IV melanoma.
- Tudriqev (vusolimogene oderparepvec-wtpg) in combination with nivolumab IV or SC for the treatment of adults with unresectable advanced cutaneous melanoma who experienced disease progression with a programmed death receptor -1 (PD-1) – blocking antibody-based regimen.

Non-Small Cell Lung Cancer (NSCLC)

- In those with resectable (tumors ≥ 4 cm or node positive) NSCLC in the neoadjuvant setting, in combination with platinum-doublet chemotherapy.
- In those with resectable (tumors ≥4 cm or node positive) NSCLC and no known EGFR mutations or ALK rearrangements, for neoadjuvant treatment, in combination with platinum-doublet chemotherapy, followed by OPDIVO Qvantig monotherapy as adjuvant treatment after surgery.
- In those with metastatic NSCLC and progression on or after platinum based chemotherapy. Patients with EGFR or ALK genomic tumor aberrations should have disease progression on FDA-approved therapy for these aberrations prior to receiving OPDIVO Qvantig.

Squamous Cell Carcinoma of the Head and Neck

- In those with recurrent or metastatic SCCHN with disease progression on or after a platinum-based therapy

Urothelial Carcinoma

- Adjuvant treatment of adult patients with UC who are at high risk of recurrence after undergoing radical resection of UC
- In those with unresectable or metastatic urothelial carcinoma, as first-line treatment in combination with cisplatin and gemcitabine

- In those with locally advanced or metastatic UC who:
    - have disease progression during or following platinum-containing chemotherapy.
    - have disease progression within 12 months of neoadjuvant or adjuvant treatment with platinum-containing chemotherapy.

Colorectal Cancer

- adult patients with MSI-H or dMMR metastatic CRC that has progressed following treatment with a fluoropyrimidine, oxaliplatin, and irinotecan, as monotherapy or as monotherapy following combination treatment with intravenous nivolumab and ipilimumab.

Hepatocellular Carcinoma

- In those with HCC previously treated with sorafenib and following combination treatment with intravenous nivolumab and ipilimumab
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Esophageal Squamous Cell Carcinoma (ESCC)

- In those with completely resected esophageal or gastroesophageal junction cancer with residual pathologic disease, who have received neoadjuvant chemoradiotherapy (CRT).
- In those with unresectable advanced or metastatic esophageal squamous cell carcinoma as first-line treatment in combination with fluoropyrimidine- and platinum-containing chemotherapy
- adult patients with unresectable advanced, recurrent or metastatic esophageal squamous cell carcinoma (ESCC) after prior fluoropyrimidineand platinum-based chemotherapy

Gastric Cancer, Gastroesophageal Junction Cancer, and Esophageal Adenocarcinoma

- In those with advanced or metastatic gastric cancer, gastroesophageal junction cancer, and esophageal adenocarcinoma in combination with fluoropyrimidine- and platinum-containing chemotherapy.

NCCN Compendia and Clinical Practice Guideline (CPG) for Opdivo Qvantig may be substituted for intravenous nivolumab. Opdivo Qvantig is not indicated in combination with ipilimumab (Yervoy). Where Opdivo has a NCCN 1 or 2A recommendation for use as monotherapy or in combination with chemotherapy, Opdivo Qvantig may be substituted.

Definitions and Measures

Adjuvant therapy: Treatment given after the primary treatment to increase the chances of a cure; may include chemotherapy, radiation, hormone or biological therapy.

BRAF: The oncogene which directions production of a protein in the regulating MAP kinase/ERKs signaling pathway, which affects cell division, differentiation, and secretion.
Colon cancer: Cancer originating in the tissues of the colon (the longest part of the large intestine). Most colon cancers are adenocarcinomas that begin in cells that make and release mucus and other fluids.
Colorectal cancer: Cancer originating in the colon (the longest part of the large intestine) or the rectum (the last several inches of the large intestine before the anus).
ECOG or Eastern Cooperative Oncology Group Performance Status: A scale and criteria used by doctors and researchers to assess how an individual's disease is progressing, assess how the disease affects the daily living abilities of the individual, and determine appropriate treatment and prognosis. This scale may also be referred to as the WHO (World Health Organization) or Zubrod score which is based on the following scale:

- 0 = Fully active, able to carry on all pre-disease performance without restriction
- 1 = Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, for example, light house work, office work
- 2 = Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours
- 3 = Capable of only limited self-care, confined to bed or chair more than 50% of waking hours
- 4 = Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair
- 5 = Dead

Immune checkpoint inhibitor: A type of drug that blocks certain proteins made by some types of immune system cells, such as T cells, and some cancer cells. When these proteins are blocked, the "brakes" on the immune system are released and T cells are able to kill cancer cells better. Examples of checkpoint proteins found on T cells or cancer cells include programmed death (PD)-1, PD-ligand 1 (PD-L1), and cytotoxic T-lymphocyte–associated antigen (CTLA)-4/B7-1/B7-2.

Karnofsky Performance Status: A scale and criteria used by doctors and researchers to assess an individual's prognosis, measure changes in their function and abilities, and determine their ability to tolerate therapies. The lower the score (from 0-100), the worse the likelihood of survival.

- 100 = Normal, no complaints
- 90 = Able to carry on normal activities
- 80 = Normal activity with effort
- 70 = Care for self. Unable to carry on normal activity or to do active work
- 60 = Requires occasional assistance, but able to care for most of his needs
- 50 = Requires considerable assistance and frequent medical care
- 40 = Disabled. Requires special care and assistance
- 30 = Severely disabled. Hospitalization indicated though death nonimminent
- 20 = Very sick. Hospitalization necessary. Active supportive treatment necessary
- 10 = Moribund
- 0 = Dead

Line of Therapy:

- First-line therapy: The first or primary treatment for the diagnosis, which may include surgery, chemotherapy, radiation therapy or a combination of these therapies.
- Second-line therapy: Treatment given when initial treatment (first-line therapy) is not effective or there is disease progression.
- Third-line therapy: Treatment given when both initial (first-line therapy) and subsequent treatment (second-line therapy) are not effective or there is disease progression.

Melanoma: A type of cancer that begins in the melanocytes. Melanoma is also referred to as malignant melanoma and cutaneous melanoma.

Metastasis: The spread of cancer from one part of the body to another; a metastatic tumor contains cells that are like those in the original (primary) tumor and have spread.

Monoclonal antibody: A protein developed in the laboratory that can locate and bind to specific substances in the body and on the surface of cancer cells.

Mutation: A permanent, transmissible change in genetic material.

Neoadjuvant therapy: Treatment given as a first step to shrink a tumor before the main treatment, which is usually surgery, is given. Examples of neoadjuvant therapy include chemotherapy, radiation therapy, and hormone therapy. It is a type of induction therapy.

Non-small cell lung cancer: A group of lung cancers that are named for the kinds of cells found in the cancer and how the cells look under a microscope. The three main types of non-small cell lung cancer are squamous cell carcinoma, large cell carcinoma, and adenocarcinoma.

Primary treatment: The first treatment given for a disease. It is often part of a standard set of treatments, such as surgery followed by chemotherapy and radiation. Also called first-line therapy, induction therapy, and primary therapy.

Programmed death (PD)-1 proteins: PD-1 proteins are found on T-cells and attach to PD ligands (PD-L1) found on normal (and cancer) cells (see immune checkpoint inhibitor above). Normally, this process keeps T-cells from attacking other cells in the body. However, this can also prevent T-cells from attacking cancer cells in the body. Examples of FDA approved anti-PD-1 agents include Keytruda (pembrolizumab), Opdivo (nivolumab), and Libtayo (cemiplimab).

Programmed death ligand (PD-L)-1: The ligands found on normal (and cancer) cells to which the PD-1 proteins attach (see immune checkpoint inhibitor above). Cancer cells can have large amounts of PD-L1 on their surface, which helps them to avoid immune attacks. Examples of FDA approved anti-PD-L1 agents include Bavencio (avelumab), Tecentriq (atezolizumab), and Imfinzi (durvalumab).

Progression free survival (PFS): The length of time during and after treatment that an individual lives but does not get worse (usually measured by the size of a tumor or amount of cancer in the body).
Progressive Disease (PD): Cancer that is growing, spreading, or getting worse.

Rectal cancer: Cancer originating in tissues of the rectum (the last several inches of the large intestine closest to the anus).

Refractory Disease: Illness or disease that does not respond to treatment.

Relapse or recurrence: After a period of improvement, during which time a disease (for example, cancer) could not be detected, the return of signs and symptoms of illness or disease. For cancer, it may come back to the same place as the original (primary) tumor or to another place in the body.

Unresectable: Unable to be removed with surgery.

Urothelial carcinoma: A type of bladder cancer which occurs in the urinary tract system.

Clinical Criteria

When a drug is being reviewed for coverage under a member's medical benefit plan or is otherwise subject to clinical review (including prior authorization), the following criteria will be used to determine whether the drug meets any applicable medical necessity requirements for the intended/prescribed purpose.

I. Individual is under 19 years of age;

OR

II. Individual has a diagnosis of ampullary adenocarcinoma; **AND**
   A. Individual has deficient mismatch repair or microsatellite instability-high [dMMR or MSI-H] disease; **AND**
   B. Individual is using in one of the following ways:
      1. As first-line therapy for intestinal metastatic disease; **OR**
      2. For disease progression if no prior immunotherapy;

OR

III. Individual has a diagnosis of anal carcinoma (NCCN 2A); **AND**
   A. Individual is using as a single agent or in combination with paclitaxel and carboplatin;

OR

IV. Individual has a diagnosis of appendiceal adenocarcinoma (NCCN 2A); **AND**
   A. Individual is using as a single agent, if no prior treatment with a checkpoint inhibitor; **AND**
   B. Individual has dMMR/MSI-H or POLE/POLD1 mutation with ultra-hypermutated phenotype [e.g., TMB >50 mut/Mb]);

OR

V. Individual is using for the treatment of bone cancer (NCCN 2A); **AND**
   A. Individual is using as monotherapy or in combination with sunitinib for dedifferentiated chondrosarcoma (NCT03277924); **AND**
   B. Individual has not received another anti-PD-1 or anti-PD-L1 agent; **AND**
   C. Individual is not receiving therapy for an autoimmune disease or chronic condition requiring treatment with a systemic immunosuppressant;

OR

VI. Individual has a diagnosis of cervical cancer (NCCN 2A); **AND**
   A. Individual is using as a single agent; **AND**
   B. Individual is using for second-line or subsequent therapy; **AND**
   C. Individual has CPS ≥ 1 for local/regional recurrence or stage IVB or recurrence with distant metastases;

OR

VII. Individual has a diagnosis of chronic lymphocytic leukemia/small lymphocytic leukemia (CLL/SLL) (NCCN 2A); **AND**
   A. Individual is using as a single agent or in combination with ibrutinib; **AND**
   B. Individual is using for histologic (Richter) transformation to diffuse large B-cell lymphoma; **AND**

OR

VIII. Individual has a diagnosis of colorectal cancer (NCCN 2A); **AND**
   A. Individual is using as monotherapy; **AND**

B. Meets one of the following;
   1. Individual has resectable disease for neoadjuvant or initial treatment (NCCN 2A); **AND**

   OR

   2. Individual is using as neoadjuvant therapy in clinical T4b disease or bulky nodal disease (NCCN 2A);

AND

C. Individual has deficient mismatch repair/microsatellite instability-high [dMMR/MSI-H] or polymerase epsilon/delta [POLE/POLD1] mutation) with ultra-hypermutated phenotype [e.g. TMB > 50 mut/Mb) (NCCN 2A); **AND**
D. Individual has not received another anti-PD-1 or anti-PD-L1 agent; **AND**
E. Individual is not receiving therapy for an autoimmune disease or chronic condition requiring treatment with a systemic immunosuppressant;

OR

IX. Individual has a diagnosis of colorectal Cancer (Label, NCCN 2A); **AND**

A. Individual is using as monotherapy in metastatic disease with either defective mismatch repair (dMMR) or high microsatellite instability (MSI-H) mutation that has progressed following treatment with a fluoropyrimidine, oxaliplatin, and irinotecan based chemotherapy; **AND**
B. Individual has not received prior immunotherapy;

OR

X. Individual has a diagnosis of uterine neoplasms, including endometrial carcinoma or uterine sarcoma (NCCN 2A); **AND**

A. Individual has a diagnosis of recurrent MSI-H or dMMR disease;

AND

B. Individual is using as a single agent; **AND**
C. Individual is using as second-line or subsequent therapy; **AND**
D. Has not received treatment with another anti-PD-1 or anti-PD-L1 agent; **AND**
E. Individual is not receiving therapy for an autoimmune disease or chronic condition requiring treatment with a systemic immunosuppressant;

OR

XI. Individual has a diagnosis of unresectable locally advanced, recurrent or metastatic esophageal squamous cell carcinoma (ESCC)(Label, NCCN 1, 2A); **AND**

A. Individual is using in combination with fluoropyrimidine- and platinum-containing chemotherapy; **AND**
B. Individual is using as first-line treatment; **AND**
C. Individual has a current ECOG performance status of 0-2; **AND**
D. Individual has no prior checkpoint inhibitor therapy or no tumor progression while on therapy with a checkpoint inhibitor; **AND**
E. Individual is not receiving therapy for an autoimmune disease or chronic condition requiring treatment with a systemic immunosuppressant;

OR

XII. Individual has a diagnosis of unresectable locally advanced, recurrent, or metastatic esophageal squamous cell carcinoma (ESCC)(Label, NCCN 2A); **AND**

A. Individual is using as single agent for second line or subsequent therapy; **AND**
B. Individual has confirmation of disease progression on or had intolerance to fluoropyrimidine- and platinum-based chemotherapy; **AND**
C. Individual has a current ECOG performance status of 0-2 or Karnofsky performance score of 60-100; **AND**
D. Individual is not receiving therapy for an autoimmune disease or chronic condition requiring treatment with a systemic immunosuppressant;

OR

XIII. Individual has a diagnosis of *completely resected* esophageal and esophagogastric junction cancers (Label, NCCN 1); **AND**

A. Individual is using as single agent for residual pathologic disease; **AND**
B. Individual has received neoadjuvant chemoradiotherapy (CRT); **AND**
C. Individual has a current ECOG performance status of 0-2; **AND**
D. Individual has not received treatment with another anti-PD-1, anti-PD-L1 agent, or other checkpoint inhibitor; **AND**
E. Individual is not receiving therapy for an autoimmune disease or chronic condition requiring treatment with a systemic immunosuppressant;

OR

XIV. Individual has a diagnosis of gastric or esophageal and esophagogastric junction cancers and has microsatellite instability-high (MSI-H) or deficient mismatch repair (dMMR) tumor (NCCN 2A); **AND**

A. Individual is using as a single agent for adenocarcinoma as postoperative management following completely resected disease in those who received preoperative therapy with intravenous nivolumab + ipilimumab; **AND**
B. Individual is not receiving therapy for an autoimmune disease or chronic condition requiring treatment with a systemic immunosuppressant;

OR

XV. Individual has a diagnosis of advanced or metastatic gastric or esophageal and esophagogastric junction cancers (Label); **AND**

A. Individual is using in combination with fluoropyrimidine or capecitabine and platinum-containing chemotherapy; **AND**
B. Individual has HER2 negative disease; **AND**
C. Individual has a current ECOG performance status of 0-2; **AND**
D. Individual has no prior checkpoint inhibitor therapy or no tumor progression while on therapy with a checkpoint inhibitor; **AND**
E. Individual is not receiving therapy for an autoimmune disease or chronic condition requiring treatment with a systemic immunosuppressant;

OR

XVI. Individual has a diagnosis of gastric or esophageal and esophagogastric Junction Cancers; **AND**

A. Individual is using for palliative care (NCCN 1, 2A); **AND**
B. Individual is not a surgical candidate OR has unresectable locally advanced, recurrent, or metastatic disease;
AND
C. Meets one of the following:
1. Has MSI-H/dMMR tumors; **AND**
2. Using as first-line therapy in combination with fluoropyrimidine- and oxaliplatin;
OR
3. Has squamous cell carcinoma; **AND**
4. Using as first-line therapy in combination with fluoropyrimidine- and platinum-containing chemotherapy;
OR
5. Using as second-line or subsequent therapy as a single agent;

AND

D. Individual has a current ECOG performance status of 0-2 or Karnofsky performance score of 60-100;
AND
E. Individual is not receiving therapy for an autoimmune disease or chronic condition requiring treatment with a systemic immunosuppressant;

OR

XVII. Individual has a diagnosis of gastric cancer (NCCN 1, 2A); **AND**

A. Individual is medically fit for surgery but with surgically unresectable disease; **AND**
1. Has MSI-H or dMMR tumors; **OR**
2. Individual is using in combination with fluoropyrimidine- or capecitabine- and oxaliplatin;

AND

B. Individual has not received treatment with another anti-PD-1 or anti-PD-L1 agent; **AND**
C. Individual is not receiving therapy for an autoimmune disease or chronic condition requiring treatment with a systemic immunosuppressant;

OR

XVIII. Individual has a diagnosis of multi-agent chemotherapy-resistant gestational trophoblastic neoplasia (NCCN 2A); **AND**

A. Individual has recurrent or progressive intermediate trophoblastic tumor or high-risk disease; **AND**
B. Individual is using as single-agent therapy; **AND**
C. Individual has not received another anti-PD-1 or anti-PD-L1 agent; **AND**
D. Individual is not receiving therapy for an autoimmune disease or chronic condition requiring treatment with a systemic immunosuppressant;

OR

XIX. Individual has a diagnosis of advanced hepatocellular carcinoma (Label, NCCN 2A); **AND**

A. Individual is using as a single agent for subsequent therapy in those who have not been previously treated with a checkpoint inhibitor; **AND**

OR

XX. Individual has a diagnosis of Histiocytic neoplasms (NCCN 2A); **AND**

A. Individual is using as first-line or subsequent therapy for primary malignant histiocytic neoplasms (MHN) as a single agent;

OR

XXI. Individual has a diagnosis of relapsed/refractory advanced classic Kaposi sarcoma (NCCN 2A); **AND**

A. Individual is using as a single agent; **AND**
B. Individual is using as subsequent systemic therapy; **AND**
C. Individual does not have multicentric Castleman Disease (MCD) or KSHV-associated inflammatory cytokine syndrome (KICS);

OR

XXII. Individual has a diagnosis of malignant pleural or peritoneal mesothelioma (NCCN 2A); **AND**

A. Individual is using as a single agent for subsequent therapy; **AND**
B. Individual has an ECOG performance status of 0-2; **AND**
C. Individual is not receiving therapy for an autoimmune disease or chronic condition requiring treatment with a systemic immunosuppressant;

OR

XXIII. Individual has a diagnosis of Cutaneous Melanoma (NCCN 1, 2A); **AND**

A. Individual is using for systemic neoadjuvant therapy; **AND**
B. Individual is using as monotherapy;

OR

C. Individual is using for systemic adjuvant therapy (NCCN 1, 2A); **AND**
D. Individual is using as monotherapy for one of the following:
    1. Stage IIB/IIC disease; **OR**
    2. C-SIT limited resectable disease; **OR**
    3. Local satellite/In-transit recurrence; **OR**
    4. Resectable nodal recurrence; **OR**
    5. Oligometastatic disease;

OR

XXIV. Individual has a diagnosis of Cutaneous Melanoma (NCCN 1, 2A); **AND**

A. Individual is using for metastatic or unresectable disease; **AND**
B. Individual is using for one of the following:
    1. First line therapy as monotherapy; **OR**
    2. Second-line or subsequent therapy as monotherapy; **OR**
    3. In combination with Tudriqev (vusolimogene oderparepvec-wtpg) for unresectable advanced cutaneous melanoma (Label);

OR

XXV. Individual has a diagnosis of metastatic melanoma with brain metastases (NCCN 2A); **AND**

A. Individual has a primary diagnosis of melanoma; **AND**
B. Using in one of the following ways:
    1. Individual has asymptomatic brain metastases (Long 2017, 2018, Tawbi 2017);

OR

2. Individual has BRAF non-specific asymptomatic brain metastases; **AND**
3. Individual is using as monotherapy;

OR

XXVI. Individual has a diagnosis of uveal melanoma (NCCN 2A); **AND**

A. Individual has metastatic or unresectable disease; **AND**
B. Individual is using as a single agent therapy;

OR

XXVII. Individual has a diagnosis of Merkel cell carcinoma (NCCN 2A); **AND**

A. Individual is using as a single agent for neoadjuvant therapy; **AND**
B. Individual is using in one of the following ways:
   1. Individual has primary clinical N0 locally advanced disease; **AND**
   2. Curative surgery and curative radiation therapy were originally deemed not feasible; **OR**
   3. Individual has primary N+, M0 regional disease;

OR

C. Individual is using as a single agent (NCCN 2A); **AND**
D. Individual is using in one of the following ways:
   1. Primary N+, M0 regional disease if curative surgery and radiation therapy are not feasible; **OR**
   2. Recurrent N+ regional disease if curative surgery and radiation therapy are not feasible; **OR**
   3. In-transit N+ regional disease; **OR**
   4. M1 disseminated disease;

OR

XXVIII. Individual has a diagnosis of non-small cell lung cancer (NSCLC) (Label, NCCN 1, 2A); **AND**

A. Individual has recurrent, advanced, or metastatic NSCLC; **AND**
   1. Individual is using as a single agent; **AND**
   2. Using for subsequent systemic therapy or subsequent progression; **AND**
   3. Confirmation of disease progression on or after platinum-containing chemotherapy; **AND**
   4. Current ECOG performance status of 0-2; **AND**
   5. Individual has no contraindications to PD-1 or PD-L1 inhibitors and no prior progression on a PD-1/PD-L1 inhibitor;

OR

B. Individual has resectable NSCLC and using as neoadjuvant therapy (Label, NCCN 2A); **AND**
   1. Individual is using in combination with platinum-doublet chemotherapy (e.g. paclitaxel and carboplatin); **AND**
   2. Resectable is defined as tumors ≥ 4 cm or node positive; **AND**
   3. Individual has no know EGFR mutations or ALK rearrangements; **AND**
   4. Individual continues with Opdivo as a single agent for adjuvant treatment after surgery;

OR

C. Individual has resectable NSCLC and using as adjuvant therapy (NCCN 1); **AND**
   1. Individual is using in combination with platinum-doublet chemotherapy; **AND**
   2. Individual is using as systemic therapy for those with resected NSCLC who received previous neoadjuvant chemotherapy plus nivolumab if no contraindications to immune checkpoint inhibitors; **AND**
   3. Individual has no know EGFR mutations or ALK rearrangements;

OR

XXIX. Individual has a diagnosis of metastatic NSCLC with brain metastases (NCCN 2A); **AND**

A. Individual has a primary diagnosis of non-small cell lung cancer; **AND**
B. Individual is using as single agent for brain metastases; **AND**
C. Individual has PD-L1 expression positive (≥ 1%) tumors;

OR

XXX. Individual has a diagnosis of renal cell carcinoma (RCC) (Label, NCCN 2A); **AND**

A. Individual has advanced or metastatic RCC ; **AND**
   1. Individual is using as monotherapy; **AND**

2. Histological confirmation of RCC with clear-cell component; **AND**
3. Individual has confirmation of disease progression after one or two prior anti-angiogenic regimens (e.g. axitinib, bevacizumab [or its biosimilar], pazopanib, sorafenib, sunitinib, etc.) for treatment of advanced or metastatic disease; **AND**
4. Current ECOG performance status of 0-2; **AND**
5. Has not received treatment with another anti-PD-1 or anti-PD-L1 agent; **AND**
6. Individual is not receiving therapy for an autoimmune disease or chronic condition requiring treatment with a systemic immunosuppressant

OR

B. Individual has relapsed, recurrent, or advanced RCC (Label, NCCN 1, 2A); **AND**
   1. Individual is using as first-line therapy or subsequent therapy in combination with cabozantinib tablets; **AND**
   2. Histological confirmation of RCC with clear-cell component; **AND**
   3. Has not received treatment with another anti-PD-1 or anti-PD-L1 agent; **AND**
   4. Individual is not receiving therapy for an autoimmune disease or chronic condition requiring treatment with a systemic immunosuppressant;

OR

C. Individual has relapse or metastatic non-clear cell RCC (nccRCC) [including hereditary leiomyomatosis and renal cell carcinoma (HLRCC)] (NCCN 2A); **AND**
   1. Individual is using as systemic therapy as a single agent or in combination with cabozantinib; **AND**
   2. Individual has not received another anti-PD-1 or anti-PD-L1 agent; **AND**
   3. Individual is not receiving therapy for an autoimmune disease or chronic condition requiring treatment with a systemic immunosuppressant;

OR

XXXI. Individual has a diagnosis of small bowel adenocarcinoma (SBA) (NCCN 2A); **AND**

A. One of the following:
   1. Advanced or metastatic disease; **OR**
   2. Locally unresectable or medically inoperable disease;

   AND

B. Individual has (deficient mismatch repair/microsatellite instability-high [dMMR/MSI-H] or polymerase epsilon/delta [POLE/POLD1] mutation with ultra-hypermutated phenotype [e.g. TMB > 50 mut/Mb])); **AND**
C. Individual is using as monotherapy;

OR

XXXII. Individual has a diagnosis of advanced or metastatic soft tissue sarcoma and aggressive soft tissue Neoplasms (NCCN 2A); **AND**

A. Individual is using as a single agent; **AND**
B. One of the following:
   1. For myxofibrosarcoma, undifferentiated pleomorphic sarcoma (UPS), dedifferentiated liposarcoma, cutaneous angiosarcoma, or undifferentiated sarcomas; **OR**
   2. For unresectable or metastatic TMB-H [≥10 mut/Mb] tumors regardless of soft tissue sarcoma sub-type;

OR

XXXIII. Individual has a diagnosis of squamous cell skin cancer (NCCN 2A); **AND**

A. Individual is using as a single agent;

OR

XXXIV. Individual has a diagnosis of squamous cell carcinoma of the head and neck (SCCHN (Label, NCCN 1):

A. Individual has recurrent, unresectable, or metastatic SCCHN; **AND**
   1. One of the following:
      a. Individual is using as monotherapy; **AND**
      b. Individual has confirmation of disease progression on or after platinum-containing chemotherapy;

      OR

      c. Individual is using in combination with cetuximab (NCCN 2A); **AND**
      d. Individual is using for first-and subsequent line therapy;

OR

XXXV. Individual has a diagnosis of head and neck cancers (NCCN 1, 2A); **AND**

A. Individual has recurrent, unresectable, oligometastatic, or metastatic Nasopharyngeal Cancers (NCCN 2A); **AND**
B. Individual has no surgery or radiotherapy (RT) options; **AND**
A. Individual is using nivolumab in combination with cisplatin and gemcitabine; **AND**
D. Has not received another anti-PD-1 or anti-PD-L1 agent;

OR

XXXVI. Individual has metastatic anaplastic thyroid carcinoma (NCCN 2A); **AND**

A. Individual is using as a single agent;

OR

XXXVII. Individual has urothelial carcinoma (Label, NCCN 1, 2A): **AND**

A. Individual has locally advanced, recurrent, or metastatic disease; **AND**
    1. Individual is using as a single agent; **AND**
    2. Individual meets one of the following criteria:
        a. Confirmation of disease progression on or after platinum-containing or other chemotherapy; **OR**
        b. Confirmation of disease progression within 12 months of receiving neoadjuvant or adjuvant treatment with platinum-containing chemotherapy;

OR

    3. Individual is using as single agent for adjuvant therapy; **AND**
    4. Individual is at high risk of recurrence after having radical resection;

OR

XXXVIII. Individual has urothelial carcinoma (Label, NCCN 1, 2A); **AND**

A. Individual has unresectable, recurrent, or metastatic disease; **AND**
B. Individual is using in combination with cisplatin and gemcitabine; **AND**
C. Individual is using as first-line treatment;

OR

XXXIX. Individual has a diagnosis of urothelial carcinoma of the Prostate (NCCN 2A); **AND**

A. Individual is using as a single agent for tumors with stromal invasion if platinum-based neoadjuvant chemotherapy not given and pT3, pT4a, pN+;

OR

XL. Individual has a diagnosis of recurrent or metastatic vaginal cancer (NCCN 2A); **AND**

A. Individua is using as a single agent; **AND**
B. Individual is using as second-line or subsequent therapy; **AND**
C. Individual has PD-L1 expression positive (CPS ≥ 1%) tumor;

OR

XLI. Individual has a diagnosis of advanced or recurrent metastatic vulvar cancer (NCCN 2A); **AND**

A. Individual is using as a single agent; **AND**
B. Individual is using as second-line or subsequent therapy; **AND**
C. Individual has HPV-related tumor.

***Note:** Actionable molecular markers include EGFR, KRAS, ALK, ROS1, BRAF, NTRK 1/2/3, MET, RET, ERBB2 (HER2), and NRG1 mutations. The NCCN panel recommends testing prior to initiating therapy to help guide appropriate treatment. If there is insufficient tissue to allow testing for all of these markers, repeat biopsy and/or plasma testing should be done. If these are not feasible, treatment is guided by available results and, if unknown, these patients are treated as though they do not have driver oncogenes (NCCN 1, 2A).

Opdivo Qvantig (nivolumab and hyaluronidase-nvhy) may not be approved for the following:

I. When Opdivo Qvantig is used in combination with intravenous ipilimumab (Yervoy); **AND**

II. When the above criteria are not met and for all other indications.

Step Therapy

Note: When Opdivo Qvantig (nivolumab and hyaluronidase-nvhy) is deemed approvable based on the clinical criteria above, the benefit plan may have additional criteria requiring the use of a preferred[1] agent or agents.

Opdivo Qvantig (nivolumab and hyaluronidase-nvhy) Step Therapy

A list of the preferred products is available here:

Requests for Opdivo Qvantig (nivolumab and hyaluronidase-nvhy) may be approved if the following criteria is met:

I. Individual is unable to use intravenous Opdivo (nivolumab) due to no venous access.

[1]Preferred, as used herein, refers to agents that were deemed to be clinically comparable to other agents in the same class or disease category but are preferred based upon clinical evidence and cost effectiveness.

Coding

The following codes for treatments and procedures applicable to this document are included below for informational purposes. Inclusion or exclusion of a procedure, diagnosis or device code(s) does not constitute or imply member coverage or provider reimbursement policy. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

HCPCS	
J9289	Injection, nivolumab, 2 mg and hyaluronidase-nvhy [Opdivo Qvantig]

ICD-10 Diagnosis	
C00.0-C06.9	Malignant neoplasm of lip, tongue, oral cavity
C09.0-C13.9	Malignant neoplasm of tonsil, oropharynx, nasopharynx, pyriform sinus, hypopharynx
C14.0-C14.8	Malignant neoplasm of other and ill-defined sites in the lip, oral cavity and pharynx
C15.3-C16.9	Malignant neoplasm of esophagus, stomach
C17.0-C20	Malignant neoplasm of small intestine, colon, rectosigmoid junction, rectum
C21.0-C21.8	Malignant neoplasm of anus and anal canal
C22.0	Liver cell carcinoma
C22.8	Malignant neoplasm of liver, primary, unspecified as to type
C22.9	Malignant neoplasm of liver, not specified as primary or secondary
C24.1	Malignant neoplasm of ampulla of Vater
C30.0	Malignant neoplasm of nasal cavity
C31.0-C31.1	Malignant neoplasm of maxillary sinus, ethmoidal sinus
C32.0-C32.9	Malignant neoplasm of larynx
C33	Malignant neoplasm of trachea
C34.00-C34.92	Malignant neoplasm of bronchus and lung
C40.00-C40.92	Malignant neoplasm of bone and articular cartilage of limbs
C41.0-C41.9	Malignant neoplasm of bone and articular cartilage of other and unspecified sites
C43.0-C43.9	Malignant melanoma of skin
C44.02	Squamous cell carcinoma of skin of lip
C44.121-C44.1292	Squamous cell carcinoma of skin of eyelid, including canthus

C44.221-C44.229	Squamous cell carcinoma of skin o ear and external auricular canal
C44.320-C44.329	Squamous cell carcinoma of skin of other and unspecified parts of face
C44.42	Squamous cell carcinoma of skin of scalp and neck
C44.520-C44.529	Squamous cell carcinoma of skin of trunk
C44.621-C44.629	Squamous cell carcinoma of skin of upper limb, including shoulder
C44.721-C44.729	Squamous cell carcinoma of skin of lower limb, including hip
C44.82	Squamous cell carcinoma of overlapping sites of skin
C44.92	Squamous cell carcinoma of skin, unspecified
C45.0-C45.9	Mesothelioma
C46.0-C46.9	Kaposi's sarcoma
C47.0-C47.9	Malignant neoplasm of peripheral nerves and autonomic nervous system
C48.0-C48.8	Malignant neoplasm of retroperitoneum and peritoneum
C49.0-C49.9	Malignant neoplasm of other connective and soft tissue
C4A.0-C4A.9	Merkel cell carcinoma
C51.0-C53.9	Malignant neoplasm of vulva, vagina, cervix uteri
C54.0-C55	Malignant neoplasm of corpus uteri, uterus part unspecified
C58	Malignant neoplasm of placenta
C61	Malignant neoplasm of prostate
C64.1-C65.9	Malignant neoplasm of kidney, renal pelvis
C66.1-C68.0	Malignant neoplasm of ureter, bladder, urethra
C69.30-C69.32	Malignant neoplasm of choroid
C69.40-C69.42	Malignant neoplasm of ciliary body
C73	Malignant neoplasm of thyroid gland
C76.0	Malignant neoplasm of head, face and neck
C79.31-C79.32	Secondary malignant neoplasm of brain, cerebral meninges
C83.00-C83.09	Small cell B-cell lymphoma
C83.30-C83.38	Diffuse large B-cell lymphoma
C83.398	Diffuse large B-cell lymphoma of other extranodal and solid organ sites
C91.10-C91.12	Chronic lymphocytic leukemia of B-cell type
C96.20	Malignant mast cell neoplasm, unspecified
C96.29	Other malignant mast cell neoplasm
C96.A	Histiocytic sarcoma
C96.9	Malignant neoplasm of lymphoid, hematopoietic and related tissue, unspecified
D09.0	Carcinoma in situ of bladder

Document History

Revised: 09/14/2026
Document History:

- 09/14/2026 – Select Review: Add FDA combination use with Tudriqev (vusolimogene oderparepvec-wtpg) for unresectable advanced cutaneous melanoma. Wording and formatting updates. Coding Reviewed: No changes.
- 09/18/2026 - Step therapy table updates.
- 09/01/2026 – Step therapy table updates.
- 06/08/2026 – Select Review: NCCN guideline updates. Add Ampullary adenocarcinoma criteria. Update Anal carcinoma for use in combination with paclitaxel and carboplatin. Update appendiceal adenocarcinoma

criteria. Specify use in only dedifferentiated bone cancer. For CLL/SLL remove mutation specific criteria and use in chemotherapy refractory or unable to receive chemoimmunotherapy. Remove POLE/POLD1 mutations specific criteria when used as monotherapy in colorectal cancer. Update Uterine neoplasms criteria with removal of usage in recurrent unresectable or metastatic TMB-H tumors. Remove induction/dysphagia duplicative criteria for Esophageal and esophagogastric junction cancer. Clarify combination chemotherapy use in metastatic gastric or esophageal and esophagogastric junction cancers. Simplify Hepatocellular carcinoma criteria. Add NCCN 2A criteria for use in histiocytic neoplasms. Update and separate out criteria for use in uveal and cutaneous melanoma. Update Merkel cell carcinoma criteria for use as a single agent in neoadjuvant therapy and as a single agent in regional disease or disseminated disease. Clarify use in NSCLC for neoadjuvant and adjuvant therapy. Remove the following disease states criteria as they are not included in NCCN, FDA guidance for Opdivo Qvantig: Hodgkin Lymphoma, Pediatric Classic Hodgkin Lymphoma, Primary Mediastinal Large B-cell Lymphoma, Extranodal NK/T cell lymphomas, and CNS –Pediatric Diffuse High Grade Gliomas. Simplified clinical criteria regarding ECOG scores, prior PD-1 and PD-L1 usage, and systemic immunosuppressants. Wording and formatting updates. Coding Reviewed: Added ICD-10-CM C24.1, C96.20, C96.29, C96.A, C96.9, and removed C71.0-C71.9, C72.0, C72.1, C72.9, C81.10-C81.99, C84.Z0-C84.Z9, C84.90-C84.99, C85.20-C85.29, C86.00.

- 06/23/2026 – Add step therapy and step therapy table.
- 04/06/2026 – Coding Update: Removed ICD-10-CM C66.0.
- 02/20/2026 – Annual Review: Separate out NCCN criteria for use in appendiceal adenocarcinoma. Add NCCN recommendation for use in Bone cancer. Clarify existing NCCN recommendations for use in NSCLC when used as neoadjuvant therapy. Update existing mutation specific language for dMMR/MSI-H or POLE/POLD1 mutation tumors. Clarify existing NCCN criteria for use in Uterine Neoplasms. Clarify existing NCCN criteria for use in gastric cancer for surgically unresectable disease. Update existing NCCN Hodgkin Lymphoma criteria for use in post-allogeneic hematopoietic cell transplant. Update existing NCCN recommendation for use in Pediatric Hodgkin lymphoma with combination use with ICE, and primary treatment in combination with AVD. Update existing NCCN recommendation for use in melanoma as a single agent if there is no evidence of disease after initial treatment with local or regional therapy. Add NCCN recommendation for use in resected advanced melanoma. Clarify existing NCCN recommendation for Merkel cell carcinoma criteria use in those who had disease progression on anti-PD-L1 or anti-PD-1. Update existing NCCN recommendation for use in NSCLC as subsequent systemic therapy or subsequent progression as a single agent. Update existing NCCN recommendation for use in Pediatric aggressive mature B-cell lymphoma when used in combination with brentuximab vedotin in relapsed/refractory disease. Update existing NCCN recommendation for use in Small Bowel Adenocarcinoma in either advanced/metastatic disease or locally unresectable or medically inoperable disease which is mutation specific for dMMR/MSI-H or POLE/POLD1. Add NCCN recommendation for use in squamous cell skin cancer. Update existing NCCN criteria for use in Pediatric Diffuse High-grade gliomas as adjuvant therapy or recurrent/progressive disease. Add new step therapy for use of Opdivo Qvantig. Coding Reviewed: Added ICD-10-CM C40.00-C40.92, C41.0-C41.9, C44.121-C44.1292, C44.221-C44.229, C44.321-C44.329 to C44.320, C44.520-C44.529, C44.621-C44.629, C44.721-C44.729, C44.82, C44.92, C47.0-C47.9, C48.0-C48.8, C49.0-C49.9 and removed C14.9.
- 08/15/2025 -Select Review: Update existing criteria to ensure TMB clarification is added to POLE/POLD1 mutations in Colorectal cancer and Small bowel adenocarcinoma. Update combination use in relapsed refractory Hodgkin lymphoma. Wording and formatting updates. Coding Reviewed: Removed ICD-10-CM C64.0 to leave code range C64.1-C65.9.
- 06/30/2025 – Coding Update: Removed ICD-10-CM C21.9 from range C21.0-C21.9 to leave only codes C21.0-C21.8.
- 05/16/2025 – Select Review: Align Opdivo updates to Opdivo Qvantig criteria. Add criteria for CLL/SLL. Clarify Colorectal cancer with FDA indication updates. Clarify use in R/R Hodgkin lymphoma and combination use with AVD. Add criteria for use in cetuximab in SCCHN and remove duplicative criteria. Coding Reviewed: Removed HCPCS NOC C9399, J9999 and all diagnosis pend effective 6/30/25. Added HCPCS J9289 effective 7/1/25. Added ICD-10-CM C00.0-C06.9, C09.0-C22.0, C22.8, C22.9, C30.0, C31.0-C31.1, C32.0-34.92, C43.0-C43.9, C44.02, C44.320, C44.42, C45.0-C46.9, C4A.0-C4A.9, C51.0-C55, C58, C61, C64.0-C68.0, C69.30-C69.32, C69.40-C69.42, C71.0-C72.1, C72.9, C73, C76.0, C79.31-C79.32, C81.10-C81.99, C83.00-C83.09, C83.30-C83.38, C83.398, C84.Z0-C84.Z9, C84.90-C84.99, C85.20-C85.29, C86.00, C91.10-C91.12, D09.0.
- 02/21/2025 – Select Review: Initial review of Opdivo Qvantig (nivolumab-hyaluronidase). Include criteria for Opdivo monotherapy and chemotherapy combination use from NCCN 1, 2A recommendations. Coding Reviewed: Added HCPCS NOC C9399 and J9999 and all diagnosis pend for Opdivo Qvantig.

References

1. DailyMed. Package inserts. U.S. National Library of Medicine, National Institutes of Health website. http://dailymed.nlm.nih.gov/dailymed/about.cfm. Updated periodically.
2. DrugPoints® System [electronic version]. Truven Health Analytics, Greenwood Village, CO. Updated periodically.
3. Lexi-Comp ONLINE™ with AHFS™, Hudson, Ohio: Lexi-Comp, Inc.; 2026; Updated periodically.
4. NCCN Clinical Practice Guidelines in Oncology™. © 2025 National Comprehensive Cancer Network, Inc. For additional information visit the NCCN website: http://www.nccn.org/index.asp. June 1, 2026.
    a. Ampullary adenocarcinoma. V2.2025. Revised January 10, 2025.
    b. Anal Carcinoma. V5.2025. Revised October 31, 2025.
    c. Appendiceal Neoplasms and Cancers. V1.2026. Revised October 30, 2025.
    d. Biliary Tract Cancers. V6.2024. Revised January 10, 2024.
    e. B-Cell Lymphomas. V1.2026. Revised December 22, 2025.
    f. Bladder cancer. V3.2025. Revised December 19, 2025.
    g. Bone cancer. V2.2026. Revised December 19, 2025.
    h. Central Nervous System Cancers V3.2025. Revised December 5, 2025.
    i. Cervical Cancer. V2.2026. Revised November 10, 2025.
    j. Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma. V2.2026. Revised December 22, 2025.
    k. Colon Cancer V5.2025. Revised October 30, 2025.
    l. Cutaneous Melanoma. V1.2025. December 20. 2024.
    m. Esophageal and esophagogastric junction cancers. V1.2026. Revised December 10, 2025.
    n. Gastric cancer. V1.2026. Revised December 12, 2025.
    o. Gastrointestinal Stromal Tumors. V1.2026. Revised January 13, 2026.
    p. Gestational Trophoblastic Neoplastic. V2.2026. Revised November 21, 2025.
    q. Head and neck cancers. V1.2026. Revised December 8, 2025.
    r. Hepatocellular Carcinoma. V2.2025. Revised October 22, 2025.
    s. Hodgkin Lymphoma V1.2026. Revised October 22, 2025.
    t. Kaposi Sarcoma. V2.2026. Revised September 16, 2025.
    u. Kidney Cancer. V1.2026. Revised July 24, 2025.
    v. Merkel Cell Carcinoma. V2.2026. Revised October 24, 2025.
    w. Malignant Pleural Mesothelioma V2.2026. Revised October 3, 2025.
    x. Malignant Peritoneal Mesothelioma. V2.2026. Revised October 3, 2025.
    y. Cutaneous Melanoma V2.2025. Revised January 28, 2025.
    z. Neuroendocrine and Adrenal Tumors. V3.2025. Revised October 1, 2025.
    aa. Non-Small Cell Lung Cancer. V3.2026. Revised December 24, 2025.
    bb. Pediatric Aggressive Mature B-Cell Lymphomas. V2.2025. Revised April 28, 2025.
    cc. Pediatric Central Nervous System Cancers. V1.2026. Revised November 25, 2025.
    dd. Pediatric Hodgkin Lymphoma. V2.2025. Revised June 9, 2025.
    ee. Rectal Cancer V4.2025. Revised October 31, 2025.
    ff. Small Bowel Adenocarcinoma. V4.2025. Revised October 31, 2025.
    gg. Small cell lung cancer. V2.2026. Revised September 16, 2025.
    hh. Soft Tissue Sarcoma. V1.2026. Revised January 16, 2026.
    ii. Squamous Cell Skin Cancer. V1.2026. Revised September 2, 2025.
    jj. T-Cell Lymphomas. V1.2026. Revised December 9, 2025.
    kk. Thyroid Carcinoma. V1.2025. Revised March 27, 2025.
    ll. Uterine neoplasms. V2.2026. Revised November 14, 2025.
    mm. Vaginal Cancer V2.2026. Revised December 4, 2025.
    nn. Uveal Melanoma. V2.2025. Revised November 6, 2025.
    oo. Vulvar Cancer. V2.2026. Revised January 6, 2026.

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CC-0281 Opdivo Qvantig

Commercial Medical Benefit

Effective Date	Preferred Agents	Non-Preferred Agents
10/01/2026	Opdivo	Opdivo Qvantig

Medicaid Medical Benefit

Effective Date	Preferred Agents	Non-Preferred Agents
09/01/2026: MD, NY, WNY 10/01/2026: WA, NJ, OH, VA 11/01/2026: CA, IA 12/01/2026: AR	Opdivo	Opdivo Qvantig

Medicare Medical Benefit

Effective Date	Preferred Agents	Non-Preferred Agents
N/A	N/A	N/A